Fabry disease: An underrecognized cause of proteinuria

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CASE PRESENTATION

A 37-year-old male was referred in 1999 for evaluation of proteinuria and a serum creatinine of 1.8 mg^{-1}. He was asymptomatic. Apart from hyperlipidemia, there was no history of diabetes, hypertension, macroscopic hematuria, or family history of renal disease or any inheritable disorder. On evaluation the patient was in good heath and a review of systems was unremarkable. His weight was 70 kg, blood pressure was 115/75 mm Hg, pulse rate was 78, and temperature was 36°C. The physical examination was remarkable because of two reddish angiectasias of about 3 mm of diameter in the trunk, which blanched under pressure and was compatible with the diagnosis of angiokeratomas. Urinalysis showed a pH of 5.4, osmolality 478 mosm kg^{-1}, protein 116 mg dl^{-1}, negative ketones, and normal microscopic findings. Twenty-four-hour urine collection showed protein excretion of 2.4 g, with a creatinine clearance of 41 ml 17:41 ml min^{-1} 1.73 m^{-2}. Serum and urine protein electrophoresis were negative for a monoclonal protein. His serum albumin level was normal at 4 g dl^{-1}. Other test results were normal or negative, including complement, antineutrophil cytoplasmic antibody, anti-DNA antibody, and hepatitis serology results. Renal ultrasound showed normal size kidneys, bilaterally. To ascertain the cause of his proteinuria, a renal biopsy was performed.

RENAL BIOPSY FINDINGS

Light-microscopy examination showed focal and segmental glomerulosclerosis (5/10 glomeruli totally sclerosed), as well as patchy interstitial fibrosis and tubular atrophy. Glomerular visceral epithelial cells showed cytoplasmic vacuolization, which was also present focally within tubular epithelial cells. No immune deposits were detected by immunofluorescence microscopy. Electron microscopy showed laminated myelin figures (zebra bodies) in glomerular visceral epithelial cells, and no immune deposits were identified. Leukocyte levels of α-galactosidase (α-Gal) were significantly reduced at 5.4%, establishing the diagnosis of Fabry disease.

GENETIC AND MOLECULAR ANALYSIS

Because of his unique presentation, genetic diagnosis was performed by using polymerase chain reaction sequencing.[1] We identified a complex mutation (insertion and deletion) A368gsX24 (1102delGinsTTATAC), which has been previously described.[1] After his diagnosis, screening for Fabry disease was offered to his only child. The father's parents were deceased at the time of diagnosis. His 17-year-old daughter was found to have the same mutation, but leukocyte α-Gal levels were 50% of normal.

CLINICAL FOLLOW-UP

Cardiac echocardiogram showed no evidence of left ventricular hypertrophy. Cranial magnetic resonance imaging disclosed two small areas suggestive of ischemic stroke. Slit-lamp examination of the eyes disclosed cornea verticillata. He was treated initially with angiotensin-converting inhibitor (enalapril 5 mg b.i.d.). Attempts to increase the dose further resulted in the development of symptomatic hypotension. Proteinuria persisted and he was started on enzyme replacement therapy (ERT) with agalsidase-beta (1 mg kg^{-1} every 2 weeks). Despite combined angiotensin-converting inhibitor and ERT, proteinuria (Figure 1) and renal disease progressed, with the patient reaching end-stage renal disease (ESRD) three and a half years after starting ERT (Figure 2). He never developed symptomatic peripheral neuropathy, vertigo, or lymphedema, and apart from angiotensin-converting inhibitor therapy he was on no other medication until late into the progression of his renal failure when erythropoietin and phosphate binder treatment was started.

DISCUSSION

Fabry disease was first described in 1898 by Johaness Fabry and William Anderson, two physicians working independently

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of each other, in Bonn and London, respectively. They described patients with 'angiokeratoma corporis diffusum', the red-purple maculopapular skin lesions characteristic of the disorder (Figure 3). After these initial cases, other associated symptoms were described and eventually the lysosome was identified as the key organelle responsible for the pathology of the disease. We now know that the disease is due to an X-linked recessive inborn error of glycosphingolipid metabolism caused by the deficient activity of the lysosomal enzyme, α-Gal A.[2] The enzymatic defect results in the progressive accumulation of neutral glycosphingolipids, (predominately globotriaosylceramide, GL-3), particularly in the vascular endothelial cells of the kidney and heart. A limited number of studies have investigated the incidence of lysosomal storage diseases (defined as the total number of cases diagnosed within a certain period of time, divided by the total number of live births in the same period). For Fabry disease, the incidence/prevalence oscillates from 1 in 40 000 to 1:117 000 in United States and Australia to 1:833 000 in Northern Portugal, the majority of them being Caucasians.[3,4] These figures are likely to underestimate the real prevalence of the disease as many patients with Fabry disease go undiagnosed due to the complexity of the diagnosis. Affected males have little, if any, α-Gal A activity, and the deposition of GL-3 occurs primarily in the lysosomes of vascular endothelial cells as well as in epithelial and smooth muscle cells throughout the body. Early clinical manifestations of the disease include angiokeratoma, acroparesthesias, episodic pain 'crises', hypohydrosis, and gastrointestinal complains. With time, progressive GL-3 accumulation in the microvasculature leads to renal, cardiovascular, and cerebrovascular manifestations such as proteinuria, renal failure, cardiac arrhythmias, and strokes leading to early death during the fourth and fifth decade of life, in affected men[4] (Table 1).

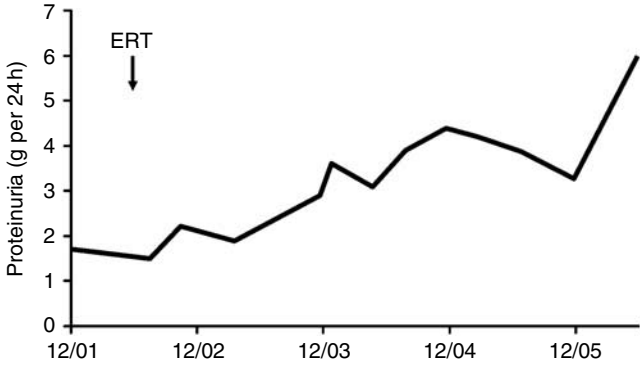

Figure 1 | Proteinuria (g 24 h^{-1}) before and after start of ERT.

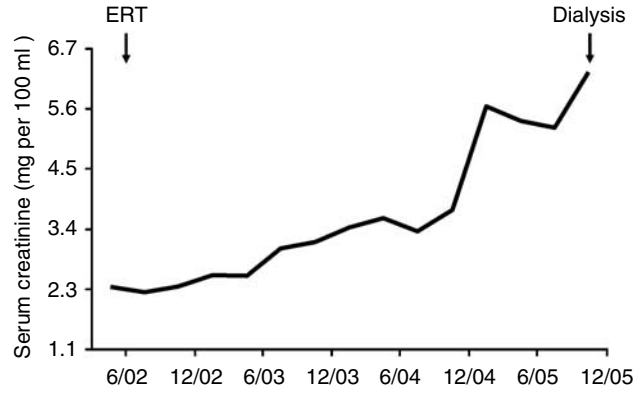

Figure 2 | Serum creatinine values before and after start of ERT.

Renal manifestations of Fabry disease are more evident in hemizygous males than in heterozygous females. However, due to non-random X inactivation, some females have a significant burden of disease, including renal failure. On gross description, the kidney may be enlarged due to accumulation of storage material. In some cases, cortical or parapelvic cysts have been demonstrated by radiographic imaging. On light microscopy, the glomerular tuft shows vacuolated glomerular cells, especially podocytes (Figure 4). Similar changes are present in the endothelial and mesangial

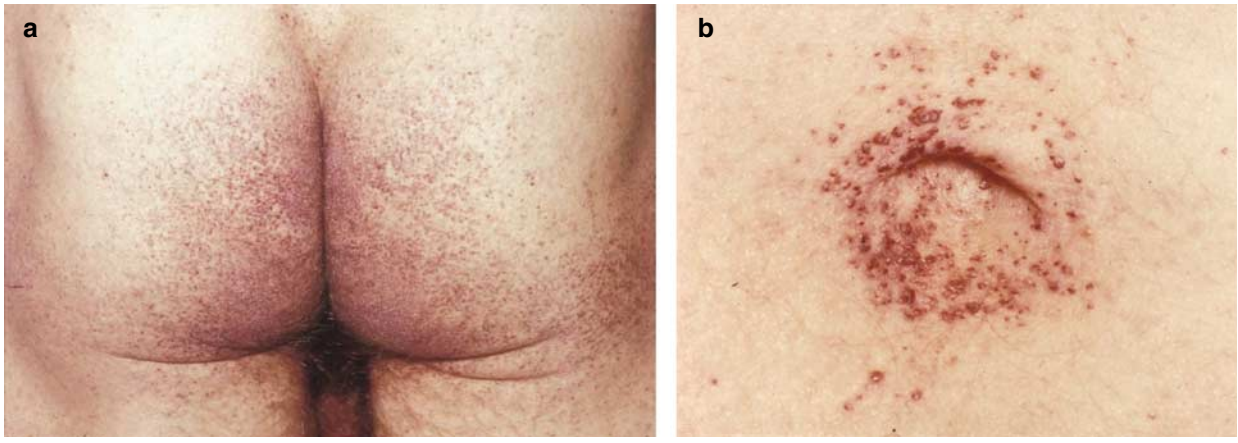

Figure 3 | Angiokeratomas: the red-purple maculopapular skin lesions characteristic of the disorder. (**a**) Skin lesions on buttocks, and (**b**) lesions on the umbilicus (provided by Dr Mark R Pittelkow, Department of Dermatology, Mayo Clinic, Rochester, MN).

Table 1 | Potential disease manifestations by average age of onset

Childhood
Episodic pain crises, acroparesthesia
Hypohidrosis
Corneal and lenticular opacities
Recurrent fever
Heat and cold intolerance
Adolescence
Angiokeratomas
Fatigue
Adulthood
Renal dysfunction
Isosthenuria, proteinuria, progressive renal insufficiency
Cerebrovascular/neurological complications
Early stroke, diplopia, dysarthria, nystagmus, nausea, vomiting, ataxia, vertigo, dizziness, hearing loss and tinnitus
Cardiac dysfunction
Left ventricular hypertrophy, coronary artery disease, arrhythmias, mitral insufficiency, congestive heart failure
Other signs/symptoms
Cornea verticillata, tortuous retinal vessels
Growth retardation, delay puberty
Impaired fertility
Episodic diarrhea, weight loss
Changes in joints and bones
Impaired social functioning
Depression
Decreased quality of life

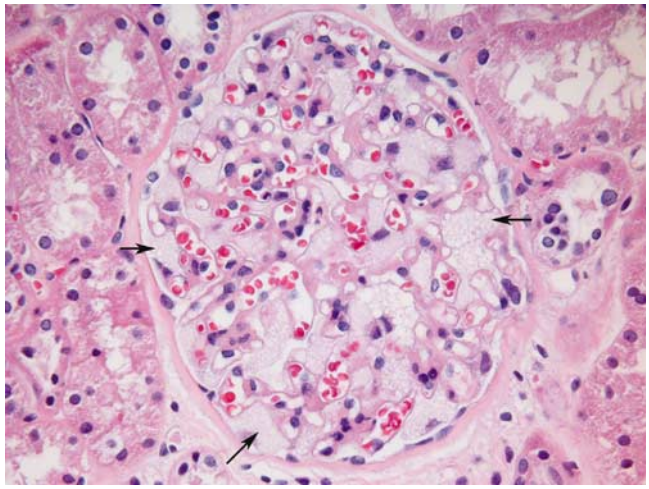

Figure 4 | Glomerulus showing vacuolated podocytes (arrows) (hematoxylin and eosin, ×400).

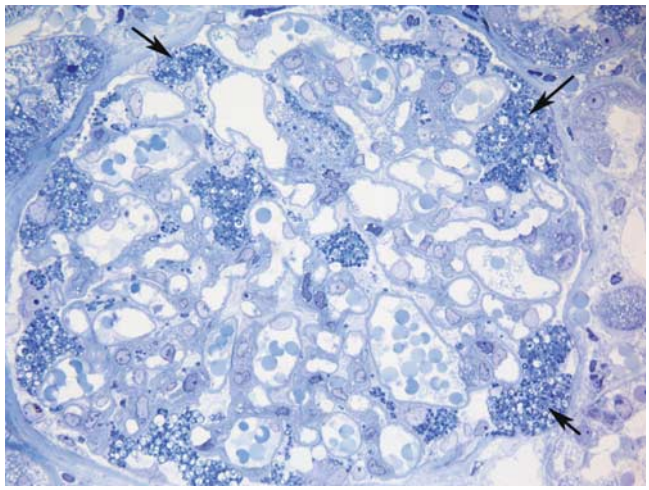

Figure 5 | Glomerulus showing enlarged podocytes containing cytoplasmic lamellated inclusion bodies (arrows) (toluidine blue, ×600).

cells, and in parietal epithelial cells of the Bowman's capsule. The vacuolated appearance is due to removal of the glycolipids during clearing and paraffin embedding of the tissue, but can be easily demonstrated in semithin sections of tissue embedded in epoxy resin and stained with toluidine blue (Figure 5). Similar cytoplasmic vacuolation can also be seen in the renal tubules, particularly in the epithelium of Henle's loop and the distal tubule. Cytoplasmic vacuolization can also be seen in endothelial cells of small arteries and arterioles, smooth muscle cells, and in interstitial cells, producing an early concentrating defect.[5] Later, progressive glomerulosclerosis manifested by proteinuria and ischemic changes in renal microvasculature result in capillary wall thickening, tubular atrophy, interstitial fibrosis, and arterial and arteriolar sclerosis. Immunofluorescence is negative. Electron microscopy shows enlarged podocytes filled with osmiophilic, granular to lamellated membrane structures (zebra bodies) (Figure 6). Accumulation of GL-3 leads to microvascular obstruction and ischemia, and ultimately renal function deteriorates with ESRD developing in the third to fifth decades of life, although cases of ESRD developing in the second decade have been reported.[6]

The case reported hereby is a patient who presented with proteinuria with no other symptoms. A renal biopsy and genetic analysis disclosed that the patient was affected by Fabry disease with preferential kidney involvement. Fabry disease presenting solely with renal involvement is rare, and only a few cases have been reported in the literature.[7–9] Nakao *et al.*[7] screened 514 unselected Japanese male patients with ESRD treated with chronic hemodialysis patients and identified six patients with Fabry disease (occurrence rate 1.2%). Among the cases reported by Nakao and co-workers, one had classic Fabry disease that was misdiagnosed, four had left ventricular hypertrophy, and only one had a normal echocardiogram. It appears that the kidney and heart are frequently involved in non-classic Fabry disease and that there are overlapping symptoms between cardiac and renal variants.[10,11] These data show that undiagnosed Fabry patients on dialysis may account from 0.25 to 1.2% of the total amount of male patients on dialysis.

Until now, all reported cases of the renal variant, including those reported by Nakao and co-workers above, are caused by missense mutations, while patients with the classical phenotype have nonsense, severe missense, frameshift, and splicing mutations that result in no enzyme protein or

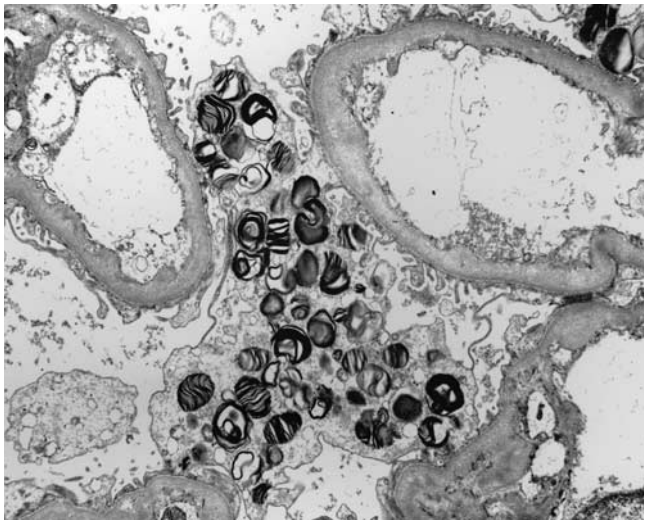

Figure 6 | Electron micrograph showing electron-dense laminated myelin figures in glomerular epithelial cells (× 5000).

mutant enzymes with very low activity. The case reported herein is produced by a frameshift mutation, with the most outstanding fact being that such a severe mutation (1102delG/insTTATAC) gives rise to a 'renal variant' of Fabry disease.

Attempting to correlate the genotype to phenotypic variations is not straightforward. Many heterozygous and some hemizygous patients show no symptoms of the disease during most of their life. Residual α-Gal A activity as well as other genetic factors may affect the phenotype. Modifying genes may include those involved in glycolipid metabolism, which may increase α-Gal substrates, thus altering the disease severity. Also, differences in intracellular factors in different cell, tissues and organs may affect the transcription rate of the α-Gal gene, which may explain why the same kind of mutation accounts for such different phenotypes. The patient reported here shows mostly renal involvement (cornea verticillata and two small angiokeratomas were the only extra-renal feature), with the diagnosis made by renal biopsy. Why having some degree of α-Gal activity can protect one organ but not the other remains to be explained. In female patients, a non-random X-inactivation limited to the kidney (skewed towards inactivation of the wild type allele) could be the reason for the outstanding phenotype.

In addition to the classical Fabry disease phenotype, and to the 'renal' variant, a 'cardiac' variant has also been identified.[11,12] These patients have residual α-Gal A activity, with GL-3 deposition confined to myocytes, and do not manifest the whole spectrum of symptoms present in classical Fabry disease.[12] Clinical presentation is usually in the fifth to the eighth decade with left ventricular hypertrophy, mitral insufficiency, and cardiomyopathy. Later in life, however, many of these patients will manifest renal involvement characterized by proteinuria without progression to ESRD.[11,12] Interestingly, the case reported by Sawada *et al.*[9] of a 'renal variant' showed the same mutation (G to A transition) as the patient reported by Sakuraba *et al.*[13] who had a cardiac variant, reinforcing the impression of idiosyncratic transcriptional rate in different organs. Although it seems reasonable to use the terms 'renal and cardiac variants' to describe these cases, we believe that the term 'extreme phenotypes' would be more precise to explain the existence of such different phenotypes. In fact, most of the reported patients with the 'renal variant' have some kind of systemic involvement, such as cornea verticillata, left ventricular hypertrophy, or neurological involvement. In all cases the involvement of other organs was minor in relation to the kidney. However, it is very important to know these cases exist in order not to miss the diagnosis in these patients.

Since Fabry disease is a potentially treatable condition, it is imperative to consider it in the differential diagnosis of any patient presenting with chronic progressive renal failure and proteinuria that cannot be readily explained by history or routine laboratory evaluation. This is of special importance in cases where there is unexplained family history of renal disease. The determination of α-Gal activity is easy and the renal biopsy shows typical changes, as described above. Screening for Fabry disease may be carried out by determining α-Gal levels in males with suggestive clinical features and/or compatible renal biopsy findings. The α-Gal A activity can easily be measured in plasma and leukocytes using the 4-methylumbelliferyl-α-D-galactopyranoside method.[14] There are fewer pitfalls in the leukocyte assay than in the plasma assay. Classically affected hemizygotes have very low or undetectable enzyme activity, but some hemizygotes may have higher residual activity in plasma and/or leukocytes. It is therefore important to confirm the mutation in these individuals. The α-Gal A activity in females can range from the low level found in affected males to the normal range, possibly due to skewed X-inactivation. Therefore, heterozygotes cannot be reliably defined by enzymatic analysis, and mutation detection is mandatory if Fabry disease is suspected. The *GLA* gene, located at Xq22.1, is 12 kb in length and contains seven exons. To date, close to 400 mutations have been described in the *GLA* gene, most of which are private missense or nonsense mutations.[15] Therefore, the whole gene must be sequenced when looking for mutation in the *GLA* gene.

Enzyme replacement therapy

Until recently, recognition of Fabry disease did not impact on the patient's prognosis, since no treatment was available. However, the availability of ERT with recombinant α-Gal has offered the promise of altering the natural history of this rare form proteinuric renal disease.[16] Currently, there are two forms of ERT available for the treatment of Fabry disease: (1) Replagal (agalsidase-alpha; Shire Human Genetic Therapies Inc., Cambridge, MA, USA) and (2) Fabrazyme (agalsidase-beta; Genzyme Corporation Inc., Cambridge, MA, USA). With the exception of the structures of the oligosaccharide

side chains, the primary amino-acid sequences of the gene products are the same.[17] The approved doses of agalsidase-alpha and agalsidase-beta are 0.2 and 1.0 mg kg^{-1}, intravenously, biweekly, respectively. In the US, only agalsidase-beta has been approved for the treatment of Fabry disease by the Food and Drug Administration, although both agents are available for clinical use in other countries.[18]

Randomized, placebo-controlled trials, and long-term, open-label extension studies of both products have consistently demonstrated that ERT reduces GL-3 levels in plasma and urine as well as glycosphingolipids accumulation in capillary endothelial cells, renal glomerular cells, and tubular epithelial cells.[19,20] In patients with relatively mild disease, the use of ERT has been able to decrease neuropathic pain, stabilize renal function, decrease left ventricular mass, and relieve gastrointestinal symptoms.[20,21] However, strokes continue to occur in some patients despite ERT.[21] Similarly, the coronary microvascular dysfunction appears not to be completely reversed by ERT.[22]

Results of a multicenter phase IV trial in which 82 patients with initial glomerular filtration rate (GFR) values <80 ml min^{-1} 1.73 m^{-2} who were prospectively randomized (2:1) to treatment with agalsidase-beta or placebo have recently been published.[23] The median time in treatment was 18.5 months and the study ended when approximately one-third of the patients had experienced a total of 27 clinical events (renal, cardiac, and cerebrovascular complications or death), 17 (63%) of which were renal events. Clinical events occurred less in the agalsidase-beta group, but the differences were not statistically significant. There was, however, an imbalance in the degree of baseline proteinuria, with patients allocated to the ERT arm having significantly higher degrees of proteinuria than those on the placebo arm, a fact that complicates the interpretation of the outcome of the study.[24] After adjustment for baseline proteinuria, the intention-to-treat analysis showed that ERT was associated with a 53% risk reduction of an event, although due to the small number of patients in the trial, the results were still not statistically significant ($P=0.058$). When the analysis was limited to the 74 patients who had no protocol violation, the 61% reduction in risk for a clinical event with ERT was statistically significant ($P=0.034$). Secondary analysis of this study showed that the benefit of ERT was greater in those patients with GFR values >55 ml min^{-1} per 1.73 m^2, but those patients with more severe renal disease did not exhibit the same benefits.[23] In this study, 12% of the patients were affected women, but the authors do not report on the outcomes on these patients. Most treatment-related events were mild or moderate infusion-associated reactions (rigors and fever), occurred in 55% of patients in the agalsidase-beta group and 23% of patients in the placebo group, and were most common during the first 6 months of treatment. One patient in the agalsidase-beta group experienced severe hypotension and had a positive serum IgE test result. Two others who had developed urticaria and rigors during infusions subsequently developed a positive skin test. Both were subsequently re-challenged and continue to receive treatment without anaphylaxis. Forty-three patients (68%) developed IgG antibodies against recombinant agalsidase-beta.[23] These antibodies tended to fall over time and do not appear to affect therapeutic efficacy.[21] Data collected from a European post-marketing follow-up survey has confirmed that ERT is safe and well tolerated in adults and children when used in a wide range of patients and in daily clinical practice, including home therapy.

Proteinuria has emerged as a major player in the development of progressive tubular injury, interstitial fibrosis, and GFR loss, including Fabry disease.[21] The higher the sustained levels of proteinuria, the faster the decline in renal function. Two studies that underscore the importance of proteinuria in Fabry patients as well as the limitations of EFR in addressing this issue have recently been published.[16] Germain *et al.*[25] provide the data on 58 patients who completed a 20-week, double-blind, randomized, placebo-controlled, phase III study of agalsidase-beta, and were transitioned to an extension trial to receive biweekly 1 mg kg^{-1} agalsidase-beta for up to an additional 54 months. Median serum creatinine and estimated glomerular filtration rate (eGFR) remained normal in the 41 patients with renal data at month 54. Six patients had renal disease progression; most (four of six) were older than 40 years and had significant proteinuria at baseline and evidence of sclerotic glomeruli pretreatment.[25] In the second study, Schiffmann *et al.*[26] evaluated whether adult male patients with Fabry disease who had demonstrated a continuing decline in GFR despite 2–4 years of conventionally dosed agalsidase-alpha therapy (0.2 mg kg^{-1} biweekly) would benefit from increasing ERT to a weekly dosing. Before switching to weekly dosing, the 11 patients who participated in the study had a mean rate of change in eGFR of -8.0 ± 0.8 ml min^{-1} 1.73 m^{-2} per year. After switching to weekly dosing, three patients demonstrated an improvement in eGFR and six patients demonstrated a slowing in the rate of eGFR decline; only two patients failed to improve their eGFR slope.[26] Although derived from a limited number of patients, these data suggest a possible dose-dependent effect of ERT. It should be noted, however, that the dosing interval used by the authors is not approved in any country where agalsidase-alpha is approved for the treatment of Fabry disease. What will be the impact of increased ERT dosing/frequency on this already very expensive therapy ($\sim$\$250 000 per year for the average adult)?

ERT in patients with end stage renal disease

The detection of Fabry patients among those receiving renal replacement therapy is also important for other organs apart from the kidney might be involved, and treatment with ERT may ameliorate symptoms or prevent further progression of cardiovascular and cerebrovascular complications. Administration of agalsidase-alpha during hemodialysis is not associated with a reduction of enzyme activity or enzyme loss into the dialysate.[27] A recent study showed that in Fabry disease patients undergoing dialysis, ERT is associated with

improvement in symptoms and slower progression of left ventricular hypertrophy.[28]

ERT in kidney transplant patients

Similarly, kidney transplantation can successfully correct the renal failure in patients with ESRD secondary to Fabry disease.[29] However, as in patients on dialysis, other aspects of Fabry disease persist and progress. Indeed, late cardiovascular and cerebrovascular complications comprise the main cause of the high morbidity and mortality in Fabry patients receiving a kidney transplant.[29] Preliminary data in small number of patients suggest that ERT is safe and often effective against extra-renal manifestations in kidney transplant patients with Fabry disease.

Angiotensin II blockade

In both diabetic and non-diabetic nephropathy patients, angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers are cardioprotective, reduce proteinuria, and slow progression of renal disease. The degree of protection is related to the degree of proteinuria reduction and if proteinuria is not lowered, the benefit is substantially attenuated. Data from the RENAAL study show that the renal protective effect of angiotensin II blockade was nearly fully explained by its antiproteinuric effect.[30] In patients with Fabry disease, proteinuria degree at the time of initiation of ERT can predict the rate of decline of GFR. ERT alone will not reduce overt proteinuria in Fabry disease, but blockade of the angiotensin II system has been shown to reduce proteinuria and to stabilize GFR.[31] It is important to keep in mind, as illustrated by the present case, that blood pressure is not typically elevated in patients with Fabry disease.[21,23,25,26] Thus, careful titration of these agents is needed, with the target being reduction of proteinuria rather than in systemic blood pressure. An ongoing prospective study in 40 Fabry patients with significant renal involvement undergoing ERT addresses the safety and efficacy of angiotensin II blockade in these patients. (http://www.clinicaltrials.gov/ct/search;jsessionid=87169CD1104ADB522E4B53168DEA01DD?term=NCT00446862&submit=Search.,%20in,%202007). The hope is that combined angiotensin II blockade together with ERT will be able to stabilize renal function in patients with more severe degrees of renal involvement.

Possible future therapies

Enzyme enhancement (chaperone) therapy. Galactose, one of the products of the enzymatic hydrolysis of GL-3, can stabilize the protein products of some missense mutations of the α-Gal A gene.[32] Similarly, pharmacological stabilization of the mutant protein can prevent premature degradation of the enzyme and has been shown to substantially increase residual α-Gal A activity.[33] Because low levels of enzyme activity ($>10\%$) appear to be protective against the development of the disease, modest increase in chaperone-induced enzyme activity might be beneficial in Fabry disease. The incomplete response to ERT in some patients with Fabry disease has been related to the inability of the enzyme to be distributed to all cell types in the body. Chaperone molecules may have a theoretical advantage over ERT because they are smaller molecules and are widely distributed to all cell types, and may cross the blood–brain barrier. Chaperone therapy is still in early research stages and is not available for clinical use.

Infusion of structurally modified α-Gal A. Under current treatments the infused enzyme is taken up mainly by vascular endothelial cells, which may limit its effectiveness. Expanding the delivery of the enzyme to all other cells by the production of several specifically targeted glycosylated forms of the enzyme, modifying the protein to allow for receptor-independent uptake or using a peptide carrier delivery system are strategies currently being proposed.[34]

Substrate reduction therapy. Agents used in substrate reduction therapy (SRT) therapy block the formation of accumulating glycosphingolipids. In the Fabry knockout mouse model, administration of the ceramide analogue D-*t*-EtDo-P4, a very potent inhibitor of glucosylceramide synthase, caused a significant reduction in renal, hepatic and cardiac GL-3.[35] In older Fabry mice, with more severe vascular involvement, recent studies showed the benefit of prolonged SRT.[36] These observations suggest that, in addition to enzymatic activity, other mechanisms are involved in the clearance of substrate in Fabry disease. Inhibitors of GL-3 formation have the advantage of being given by mouth and may enhance the effect of ERT. Combined therapy may be especially relevant to the kidney since SRT appears to cause uniform reduction of accumulated GL-3, whereas only specific cell types appear to respond favorably to ERT.[34]

Gene therapy. Transduction of hematopoietic cells with a retrovirus encoding α-Gal A to α-Gal A-deficient mice resulted in enhanced α-Gal A as well as a decrease of GL-3 storage in all organs and tissues except the brain.[37] Similarly, long-term correction of the α-Gal A deficiency was obtained using different adeno-associated viral vectors.[38] Maintenance of gene expression long-term as well as safety issues remain major obstacles in translation into human studies. Additional problems include the immune response that may lead to clearance of and/or loss of enzyme activity.

Infusions of structurally modified α-Gal A. In patients with Fabry disease, the bulk of infused α-Gal A is taken up by vascular endothelial cells, thus limiting its effectiveness. Development of several specifically target glycoforms of the enzyme or enzyme modification by adding the TAT protein transduction domain, thus allowing for receptor-independent cellular uptake, has been proposed as a way to increase delivery of α-Gal to other cells.[39]

CONCLUSION

There are some forms of Fabry disease in which renal involvement is most outstanding and together with the cardiac variant, represent extreme phenotypes of a single disorder. It is of great interest for nephrologists to know the existence of this type of patient, since the diagnosis might be difficult due to a lack of typical signs and symptoms of Fabry disease. The

advent of ERT has transformed Fabry disease in a potentially treatable cause of proteinuric chronic renal disease. However, some issues are still unresolved: a therapeutic benefit on the cerebrovascular aspect of the disease remains to be demonstrated. It is likely that the benefit of ERT is the same in female as in male patients, but we do not know for sure. This is an important issue, for females represent 12% of Fabry patients on ERT. When should treatment be started? In childhood? As soon as the diagnosis is made? Or should we wait until renal function starts to decline? In the future, better results may be achieved with the use of modified enzyme preparations, SRT, chaperone therapy, combination therapies, or others still in the development phase. Until then, the available evidence strongly suggests that ERT can improve renal function and/or slow the decline of GFR in patients with Fabry disease and mildly to moderately reduce GFR. However, as illustrated by the present case, progression of disease might occur despite treatment, particularly if ERT is initiated late in the progression of the renal disease. The current thinking is that the sooner ERT is started, the more likely renal disease progression will be avoided. Further studies are needed in order to confirm these observations, and some have already been initiated.

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